

AVX754 (apricitabine)



Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

AVX754, previously known as SPD754 and now known as apricitabine, is a nucleoside reverse transcriptase inhibitor (NRTI). AVX754 is the negative enantiomer of a member of the 4-thio heterosubstituted nucleoside analogue class. It is a novel cytidine analogue with activity against HIV strains that are resistant to other NRTIs. [1] [2]

HIV/AIDS-Related Uses

AVX754 is a deoxycytidine analogue entering Phase IIb studies for the treatment of HIV infection. It is being studied as a first choice, second regimen drug for the treatment of HIV infection in people who have failed treatment with lamivudine. AVX754 received fast-track approval status from the FDA.[3] [4]

Pharmacology

AVX754 selectively inhibits the HIV replication enzyme reverse transcriptase (RT) in the same manner as traditional NRTIs. AVX754 is the negative enantiomer of a failed investigational racemic mixture NRTI and appears to retain pharmacodynamic activity with reduced toxicity. The drug does not convert to the positive enantiomer or racemic mixture in vivo.[5] [6] [7]

AVX754 must be metabolized to triphosphate form for antiviral activity. Intracellular concentrations of the active triphosphate are proportional to plasma concentrations of AVX754. AVX754-TP accumulates intracellularly with twice-daily dosing, has a half-life of 6 to 7 hours, and achieves maximum plasma concentrations (C_{max}) at approximately 4 hours post-dose.[8] In Phase I studies, oral bioavailability was 65% to 80% with 1,600 mg to 400 mg single doses, respectively, and was unaffected by food. AVX754 is rapidly absorbed. The time to peak plasma concentration ranged from 1.5 to 1.7 hours and was unaffected by dose or gender. The drug appears to penetrate the cerebrospinal fluid. AVX754 exhibits linear pharmacokinetics following administration of single and multiple doses. AVX754 is primarily excreted renally; elimination is unaffected by

gender. Most of the parent drug is excreted within the first 8 hours.[9] [10]

Resistance to AVX754 develops slowly, compared to other NRTIs such as lamivudine, and is associated with the K65R, V75I, and M184V mutations. AVX754 is active against zidovudine- and lamivudine-resistant viruses.[11] The presence of 5 thymidine analogue mutations (TAMs) resulted in a less than twofold median change in AVX754 activity. No new resistance-conferring mutations emerged after 10 days of monotherapy; patients with baseline nucleoside analogue mutations showed promising decreases in viral load.[12]

A 10-day Phase IIa trial in 63 HIV infected, treatment-naïve patients compared daily doses of 400 mg to 1,600 mg AVX754. Viral load decreased more than 25-fold, even in the presence of nucleoside-associated mutations.[13]

A Phase IIb dose-ranging trial in treatment-experienced HIV infected patients is ongoing to determine AVX754 activity in patients with HIV strains resistant to lamivudine and with the M184V mutation. Responses to doses will be compared to each other and to lamivudine for 21 days and 24 weeks.[14]

Adverse Events/Toxicity

Unlike its racemic mixture predecessor BCH-10652, AVX754 showed little sign of mitochondrial toxicity in an early safety study in monkeys. After 52 weeks of 100 mg/kg/day treatment with AVX754, mild but reversible hyperpigmentation, gastrointestinal effects, and minimal red blood cell count changes were observed. No bone marrow or mitochondrial abnormalities occurred in the liver, heart, or skeletal muscle.[15] [16] In a dose-ranging study in 63 HIV infected patients, all dosages were well tolerated.[17] No evidence of mitochondrial toxicity has been observed in vitro at concentrations 30 times greater than C_{max}. [18]

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Drug and Food Interactions

AVX754 displayed additive to synergistic antiviral activity in vitro against wild type HIV-1 when combined with a range of antiretrovirals.[19] Specifically, AVX754 and lamivudine had additive antiviral activity but shared a common anabolic pathway. In a Phase I study which combined AVX754 and lamivudine, lamivudine reduced intracellular AVX754-TP concentrations in a dose-dependent manner by four- to sixfold relative to the AVX754-TP concentration alone. AVX754 had no effect on lamivudine or lamivudine triphosphate concentrations.[20] [21]

Clinical Trials

For information on clinical trials that involve AVX754 (apricitabine), visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: AVX754 (apricitabine) AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[22]

Dosage Form: AVX754 is manufactured in capsule form.[23] AVX754 has been studied at doses of 200, 400, 600, and 800 mg twice daily and at doses of 800, 1,200, and 1,600 mg once daily.[24] [25] No apparent differences have been seen between daily and twice daily dosing schedules. The twice daily dosing schedule provides adequate and sustained intracellular accumulation and has been chosen as the primary schedule for continued study; once daily dosing may be determined in later trials.[26]

Chemistry

CAS Name: 2(1H)-Pyrimidinone,

AVX754 (apricitabine)



Chemistry (cont.)

CAS Number: 160707-69-7[28]

Molecular formula: C₈H₁₁N₃O₃S[29]

C45%,H5%,N20%,O22%,S8%[30]

Molecular weight: 215.0[31]

Other Names

(-)dOTC[32]

BCH10618[33]

Apricitabine[34]

Further Reading

Bethdeed et al. In vitro activity of SPD754, a new deoxycytidine nucleoside reverse transcriptase inhibitor (NRTI), against 215 HIV-1 isolates resistant to other NRTIs. *Antivir Chem Chemother.* 2005;16(5):295-302. PMID: 16245645

Otto MJ. *Curr Opin Pharmacol.* 2004 Oct;4(5):431-6. PMID: 14508885

Manufacturer Information

AVX754 (apricitabine)
Avexa Limited
576 Swan Street
Richmond Victoria, Australia
61-3-9208-4300

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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